REMARKS

Amendments to the Specification

Applicants have amended the specification in the first paragraph to perfect the priority claims. Specifically, Applicants have removed the claims to priority to U.S. Patent Application No. 10/427,160 and International Patent Application No. PCT/US02/15876, and by doing so, expressly disclaim priority therefrom. The amendment does not add any new matter.

Amendments to the Claims

Claims 1, 14, 19, 20, 21, 32, 33, 34, 39-42, and 44 have been amended. Claims 2-13, 15, 18, 22-29 were previously canceled. Claims 46 and 47 have been canceled herein without prejudice or disclaimer. New claims 48 and 49 have been added. Accordingly, claims 1, 14, 16, 17, 19-21, 30-45, 48 and 49 are currently under consideration.

Claim 1 has been amended in parts c. and d. to remove certain redundancies, and in parts e. and f. to recite "e. 50 percent or more of the nucleotides in each strand are chemically modified; and f. any of the purine nucleotides are differentially modified at a 2'-sugar position from any of the pyrimidine nucleotides at a 2'-sugar position."

Claims 14, 19, 20, 32, 33, 34 have been amended to replace each recitation of "1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more" with "1 or more."

Claim 21 has been amended to delete the word "terminal."

Claims 39- 41 have been amended to delete the word "further."

Claim 42 has been amended to clarify that one or more of the nucleotides present in the sense strand, the antisense strand, or both the sense strand and antisense strand, are 2'-O-methyl modified nucleotides.

Claim 44 has been amended in part c. to provide the name of the target gene; amended in part e. to recite 35% modification and delete 50% modification, and to include "phosphorothioate" modification; amended in part f. to delete the word "sugar";

and amended in part g. to recite that at least two of the modifications are different from each other.

The pending claims are fully supported by the application as filed and various priority applications, such as, for example, PCT/US03/05028 and 60/363,124. To expedite prosecution, a representative but non-exhaustive list of support from the instant application and these priority applications are provided below.

Claim No.	**Support from U.S. Appl. No. 10/798,090**	**Support from PCT/US03/05028**	**Support from U.S. Appl. No. 60/363,124**
1(a)	11:28 -12:3,17:11-17, Fig. 4	9:20-26, 10:12-16, Fig. 18	12:4-8
1(b)	21:16-20, 34:17-20	23:15-23	12:4-8
1(c)	21:21-28, 22:1-16, 34:17-20, Table I and III	8:21-30, 9:20-26, Table V	12:4-8, 18:1-5, Table III
1(d)	21:21-28, 22:1-16, 34:17-20	8:21-30, 9:20-26	12:4-8, 15:15-21
1(e)	13:14-26, Tables III and IV, Fig. 4	14:6-10, 14:19-30, Tables I and IV, Fig. 18	5:13-17, 10:3-15, 10:31-11:11, Table I
1(f)	17:17-26, Tables III and IV, Fig. 4	27:25-30:20, 35:9-36:10, 16:26-17:26, Tables I and IV and Fig. 18	6:19-7:11, 10:17-25, 10:3-17, Table I
14	17:17-24, 23:1-3, 40:13-30, 42-44	16:26-16:26, 27:28-28:2	6:19-7:11, 5:14-17, 10:3-11, 17-25
16	104:14 – 105:15, 32-33, 42-44	20:30-31, 21:16-17, 22;2-3, 68:17-18	10:3-11, 10:17-25
17	17-19, 37:23 – 39:2, 40:1-4, 42-44	10:19-20, 29:13-14, 31:14-16, 86: 16-31	8:21-25, 13:18-14:9
19	17:24-26, 23:10-13, 32-33; 41:23- 42:11, 42-44	16:26-17:26, 35:15-18	6:19-7:11, 10:31-11:25
20	17:24-26, 32-33; 42:12-20,	16:26-17:26, 28:30-	6:19-7:11, 10:31-

Claim No.	Support from U.S. Appl. No. 10/798,090	Support from PCT/US03/05028	Support from U.S. Appl. No. 60/363,124
	42-44	29:2, 35:32-36:3,	11:25
21	25:26-28	10:30-11:2, 15:3-4, 19:11-20:2, 29:23-27	8:26-9:13, 9:23-25
30	20:22-23, 24:18-19	11:20-21, 19:11-20:2	8:26-9:13
31	25:9-10	45:4-9, 90:12-44	45:32-46:13
32	17:17-20, 32-33, 42-44	16:26-17:26, 22:10-15, 22:27-23:2	6:19-7:11, 10:3-11, 17-25
33	17:17-24, 18:10-20, 18:28 – 19:7, 23:1-5, 32-33; 40:13-30, 41:3-22, 42-44, 42-44	16:27-17:26, 22:10-12, 27:23-28	6:19-7:11, 10:1-30
34	17: 24-26, 18:10-20, 18:28 – 19:7, 23:5-7, 32-33; 41:23-42:11; 42:12-20	16:26-17:26, 28:3-9, 28:13-19, 28:24-30	6:19-7:11, 6:19-7:11, 10:3-16,10:25-30 10:31-11:25
35	14:3-4, 16:18-20, Fig. 4 & 5	8:21-22, 30:2-4, Tables I and IV, Fig. 18	35:29-31, Table I
36	32-33,42-44	116:26-17:26	6:19-7:11, 10:3-11, 10:17-25
37	20:6-20, 23:29 – 24:3	13:11-14, 19:24-25, 23:24-25, 29:23-26, 69:15-20	4:9-11, 9:7-10, 12:4-13
38	24:1-5, 30:7 – 31:3	14:6-10, 66:28-30,	5:13-17, Table I
39	26:18 – 27:22, 31:4-26, 32-33, 42-44	20:3-25	9:14-10:2, 11:6-11
40	44:24-27	31:28-32:6	
41	40:5-8, 44:24-26	31:28-32:6, 36:17-20, 83:26-30	37:28-31
42	11:28 -12:3,17:11-17, Fig. 4, 21:16-20, 21:21-28, 22:1-16, 34:17-20, 17:24-26, 23:10-13, 32-33; 41:23- 42:11, 42-	8:15-19, 8:21-30, 9:1-5, 9:6-13, 9:20-26, 10:4-11, 10:13-15, 12:13-15, 13:3-6,	3:15-17, 5:14-17, 6:19-7:12, 10:3-11:25, 12:4-9, 18:1-5, 19:11-14, 24:15-

Claim No.	Support from U.S. Appl. No. 10/798,090	Support from PCT/US03/05028	Support from U.S. Appl. No. 60/363,124
	44, Tables III and IV, 104:14 – 105:15, 18:10-20, 18:28 – 19:7, 23:5-7, 42:12-20	14:3-10, 16:26-17:27, 20:30-31, 21:15-17, 22:2-3, 23:15-20, 28:3-23, 29:3-20, 29:28-30:10, 68:16-18, Table V, Fig. 18	22, 35:29-30; Table 1 & III
43	25:9-10	45:4-9, 90:12-14	45:32-46:13
44	11:28 -12:3,17:11-17, Fig. 4, 21:16-20, 21:21-28, 22:1-16, 34:17-20, 17:24-26, 23:10-13, 32-33; 41:23- 42:11, 42-44, Tables III and IV, 104:14 – 105:15, 18:10-20, 18:28 – 19:7, 23:5-7, 42:12-20 13:1-13	8:15-19, 8:21-30, 9:1-5, 9:6-13, 9:20-26, 10:4-11, 10:13-15, 12:13-15, 13:3-6, 14:3-10, 14:19-24, 16:26-17:27, 23:15-20, 28:3-23, 29:3-20, 29:28-30:10, Table V, Fig. 18	3:15-17, 5:14-17, 6:19-7:12, 10:3-11:25, 12:4-9, 18:1-5, 19:11-14, 24:15-22, 35::29-30; 42:4-16, Table 1 & III
45	25:9-10	45:4-9, 90:12-14	45:32-46:13
48	17:24-26, 23:10-13, 32-33; 41:23- 42:11, 42-44, 17: 24-26, 18:10-20, 18:28 – 19:7, 23:5-7, 32-33; 41:23- 42:11; 42:12-20, 17:17-24, 18:10-20, 18:28 – 19:7, 23:1-5, 32-33; 40:13-30, 41:3-22,	28:3-23, 29:3-30:20, 35:9-25	6:19-7:11, 10:17-25, 10:3-17
49	32-33, 42-44	14:6-10	5:13-17

Additional support can be found elsewhere in the applications.

Amendments to and cancellations of the claims are made without prejudice or disclaimer and do not constitute amendments to overcome any prior art or other statutory rejections. They are fully supported by the specification as filed and by the priority applications, as explained above, and thus do not introduce new matter. These amendments and cancellations are not and should not be construed as admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in other

appropriate applications. Accordingly, Applicants respectfully request the entry of the amendments presented herein.

Restriction Requirement

The Office withdrew claims 46 and 47, alleging a constructive election by the Applicants of the product claims, based on prior prosecution on the merits. Office Action at pages 3-5. The Office has also required restriction between the product and process claims. Applicants have canceled claims 46 and 47 in the present submission, thereby rendering this requirement moot.

Withdrawal of Previous Rejections

The Office found Applicant's amendments and/or arguments filed on 10/18/07 with respect to the Double Patenting rejection and the rejection under 35 U.S.C. 103(a) persuasive. Office Action, at page 5. Applicants acknowledge the withdrawal of these rejections.

Priority

While according claims 1, 14, 16, 17, 19-21, 30-38, 42 and 43 the priority date of February 20, 2003, on which PCT/US03/05028 was filed, the Office declined to afford the same or earlier priority to newly added claims 39-41, 44 and 45, as those latter claims were allegedly not supported by PCT/US03/05028 or earlier priority documents.

Specifically, the Office stated that neither PCT/US03/05028, nor any earlier priority applications, teaches a limitation where, in addition to the claimed percentages and types of modifications of claim 1, the molecule "further" includes the modifications recited in claims 39-41. Without acceding to the merits of the Office's argument, the instant claims have been amended to remove the word "further." As such, the recited chemical modifications are fully supported in the as-filed and earlier applications.

The Office also stated that neither PCT/US03/05028 nor any prior-filed applications teaches a limitation wherein each strand has "no more than 3 consecutive ribonucleotides," as recited in claims 44 and 45. Without acceding to the merits of this contention, claim 44 has been amended to recite "at least two of said modifications are

different from each other." Support for the recited molecule is found in the instant specification and the earlier-filed priority applications, as indicated above.

Further, the Office declined to afford the instant claims a priority date of March 11, 2002, on which Application 60/363,124 (the '124 application) was filed because the '124 application allegedly does not support (1) the instant limitations of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 "or more" of each of the specific modifications; (2) "one to ten or more" of each of the specific modifications; (3) the instant limitation of "further" including modifications in excess of the percentages recited in claim 1; or (4) the limitation "no more than 3 consecutive ribonucleotides". Office Action, at page 6. Applicants have amended the relevant claims to recite "1 or more," which was clearly and fully supported by the instant application and the priority applications. As such, Applicants urge that the instant claims are entitled to a priority date of March 11, 2002.

Rejections under 35 U.C.S. § 112, first paragraph

Claims 39-41, 44 and 45 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office asserted that the instant specification does not teach a limitation of a molecule of claim 1 "further" including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of a particular modification. Without acquiescing to the propriety of the Office's contention, and solely to advance prosecution, Applicants have amended these claims to remove the term "further," thereby obviating the Office's concerns. The Office also took issue with the phrase "has no more than 3 consecutive ribonucleotides" recited in claim 44, as it was allegedly not disclosed in the instant specification and therefore constituted new matter. Without acquiescing to the propriety of the Office's contention but solely to advance prosecution, Applicants have amended claim 44 so that it no longer recites "has not more than 3 consecutive ribonucleotides." With these amendments, Applicants submit that the new matter rejection is moot and respectfully request withdrawal of the 35 U.C.S. § 112, first paragraph, rejection.

Claims 1, 14, 16, 17, 19-21, and 30-35 were also rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Specifically, the Office alleged that "[a]lthough the specification discloses examples of nucleic acid sequences with chemical modifications (tables and figures), the specification does not describe a sufficient number of nucleic acid [sic] that are chemically modified at about 50 to 100% of the nucleotides of each strand with the instantly recited modifications or combination of modifications that result in active molecules to describe the instant genus". Office Action, at page 9. The Office further alleged that "applicant has not described a single nucleic acid molecule that is 100% chemically modified with the instant configuration of modifications that retains activity." *Id*. at page 10. The Office finally argued that "the extensive chemical modification that is instantly recited introduces an extra level of uncertainty" and stated that one of ordinary skill in the art would not be able to envision which molecules would result in active molecules because the Applicant has not provided any activity of the genus of molecules. *Id.* Thus, the Office concluded that the ordinary skilled artisan would not recognize that the Applicant was in possession of the claimed genus at the time of filing.

Applicants respectfully disagree. As acknowledged by the Office, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention. *See, e.g.,* MPEP 2163(I). On the other hand, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. MPEP 2163(I)(A) (citing *In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976)). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); MPEP 2163.04. The MPEP Further provides that possession can be demonstrated "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *Id.*

Contrary to the Office's allegations, the specification indeed fully describes the physical and chemical properties of the claimed molecules. For example, the specification describes double-stranded nucleic acid molecules having a sense strand and antisense strand

where the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence or portion of sequence of the CHRM3 gene and the sense strand comprises a nucleotide sequence substantially similar to a CHRM3 gene or a portion thereof. Specification, at pages 10-12, 14. The nucleic acid may or may not have ribonucleotides. *Id.*, at page 16. In various embodiments, the nucleic acid molecules are about 19 to about 29 nucleotides in length. *Id*, at page 11. In certain other embodiments, the nucleic acid molecules have about 19 base pairs and about 1-3 nucleotide overhangs or blunt ends. *Id.*, at pages 12, 14, 15, 20. The specification further provides nucleotide sequences of exemplary antisense strands and sense strands. *Id.,* at pages 10-11.

The specification also teaches various chemical modifications. For example, the specification teaches that the nucleic acid molecules claimed herein can have phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides, "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and inverted deoxy abasic residues and further teaches the percentage modification of the molecules, including about 5% to about 100% modified nucleotides. *Id.,* at pages 12 and 13. It teaches specific chemical modifications on purine and pyrimidine nucleotides and further teaches on which particular strand the chemical modifications are found. *Id.,* at pages 17-19, 23, Figures 4, 5, 10, Table IV. In addition, the specification even describes in detail numerous examples of nucleic acid molecules having specific chemical modifications. *Id., at* pages 31-34. It further provides the structures of many exemplary nucleic acid molecules targeting CHRM3 RNA, including sequences and modifications. *See id.,* at Tables II, III.

To address the Office's allegations that applicants have not described a single nucleic acid molecule that is 100% chemically modified, Applicants respectfully point out that, in Table III, numerous chemically modified nucleic acid molecules having 100% modification are provided, see, *e.g.* the nucleic acid molecules having SEQ ID NOs: 239 – 270. Informed with the structural features, those skilled in the art are able to envision the claimed modified nucleic acid molecules and would know Applicants had possession.

Furthermore, the specification provides extensive guidance on how to make and select the claimed molecules. For example, it teaches how to synthesize the nucleic acid

molecules at pages 95-99. It further teaches how to chemically modify the nucleic acid molecules on pages 99-108. It does not stop there, but then describes how to identify potential siRNA sites and select siRNA sites in CHRM3 RNA at pages 123- 129, where chemical modifications are introduced into the siNA construct based on educated design parameters, and the modified construct is then tested in an appropriate biological system and in parallel in, for example, a cell culture system. As such, the specification describes methods of testing siRNA activity *in vitro*, in cell culture, and in animal models.

Finally, the specification describes the functional characteristics of the claimed molecules. For example, it teaches that these molecules can be used to modulate the expression of cholinergic muscarinic receptor genes, including the CHRM3 gene. *See id.,* at page 8, lines 10-16; pages 21, 49-55. The molecules can also be used to treat respiratory and/or pulmonary disorders. *See id.,* at page 9.

On the other hand, the Office maintained that Applicants has not described a structure that would lead one of ordinary skill to construct only those molecules that are active. It is respectfully noted, however, that the instant claims do not recite nucleic acid molecules that are "functional" or "active." Applicants submit that it is improper and contrary to patent law to import such functional limitation into the claims where none exists. Thus, descriptions that lead to only active constructs should not be required.

Countering the Office's assertion that there is an insufficient number of examples to support the claims, Applicants respectfully point out the considerable number of representative examples in the instant specification. Furthermore, Applicants submit that the written description requirement does not require an actual reduction to practice. MPEP 2163 (II)(A)(3)(a). Having not only described but also reduced to practice the large number of molecules in Table III, Applicants believe that the written description requirement is satisfied.

The Office's concern that the specification does not describe a sufficient number of species with a sufficient number of chemical modifications to support the genus is also unwarranted because an applicant is not required to set forth a description of the complete structure of every species within a chemical genus. *See Utter v. Hiraga,* 845 F.2d 993 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 USC § 112, paragraph

1, contain a written description of a broadly claimed invention without describing all species the claim encompasses.")

Thus, contrary to the Office's allegations of lack of written description, the instant claimed invention has been adequately described in a way that would convey with reasonable clarity and certainty to those skilled in the art that Applicants were in possession of the claimed invention. Accordingly, Applicants respectfully request withdrawal of the written description rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 14, 16, 17, 19-21, and 30-45 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Nyce (WO 99/13886), Braasch *et al.* (Biochemistry, 2002 Vol. 41:4503-4510), Matulic-Adamic *et al.* (US 5,998,203), Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Kurreck *et al.* (Nucleic Acids Research 2002, Vol. 30 No. 9, pages 1911-1918), Bertrand *et al.* (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004), and Olie *et al.* (Biochimica et Biophysical Acta, 2002, 1576, pages 101-109). Applicants respectfully traverse.

Elbashir allegedly teaches chemically modified (2'-deoxy and 2'-O-methyl) siRNAs with a separate sense and antisense strand, wherein each strand is 21-23 nucleotides and at least 19 nucleotides of the sense stand are complementary to the antisense strand. Office Action, at page 14. Elbashir allegedly further teaches modification of 19% of the nucleotides in a 21 nucleotide long duplex, which constitutes "about 50" percent. *Id.* The Office alleged one would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir wherein the nucleic acid is specific for CHRM3 RNA comprising SEQ ID NO:305, because Nyce teaches antisense oligonucleotides targeted to CHRM3 and Bertrand teaches that siRNA is more efficient than antisense. Furthermore, the Office alleged that one would be motivated to incorporate the modifications taught by Nyce, Elbashir, Parrish, Matulic-Adamic, and Kurreck, "as well as various combinations of these modifications," into the siRNA duplex

of Elbashir, because these modifications "were known in the art to protect nucleic acids from exonuclease degradation and enhance the activity of nucleic acids." *Id.* at page 19. The Office further asserted that Elbashir offers motivation to test various types of known chemical modifications at about 50 to 100% of the nucleotide positions of each strand because Elbashir teaches successful inhibition of "about 50" percent of the nucleotides (8/42) and teach testing two types of chemical modifications extensively in siRNA molecules, and Parrish and Matulic-Adamic teach extensive chemical modification of nucleic acids with successful inhibition of target gene expression. *Id.* at 21. The Office believed that the specific configurations and percentages of known chemical modifications could have been attained by "routine optimization." *Id.* at 23. Finally, the Office asserted one would have a reasonable expectation of success given that the modifications were known in the art . . . to add benefits to antisense oligonucleotides, ribozymes, or siRNA duplexes, as evidence by Elbashir, Nyce, Kurreck, Matulic-Adamic, Parrish, Braasch and Olie. *Id.*, at 24.

In response, Applicants note that Olie, Braasch, Bertrand and Kurreck are not proper prior art to the instant claims as these references were published after the priority date of the '124 application. As such, the instant claims are not obvious over the cited references.

Moreover, the Office's description of at least some of the cited references is incomplete or inaccurate. Specifically, although noting that, according to Elbashir, complete (100%) substitution of one or both strands abolished RNAi activity, the Office neglected to mention the express teaching of Elbashir that:

> [m]ore extensive 2'-deoxy [aside from substitutions of the 2 nt 3'-overhanging ribonucleotides] or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Elbashir, at page 6885, left column. Therefore, Elbashir not only teaches away from 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications, but also teaches away from <u>any</u> modifications beyond incorporation of up to four 2'-deoxy modifications at the 3'-end of each strand in a 42 nt duplex. Because 19% cannot

be reasonably extended to cover "about 50%" and surely cannot be said to cover "50%," Elbashir does not teach 50% modification on each strand.

The summary of Parrish *et al.* is incomplete as well. For example, the Office alleged that Parrish teaches a chemically synthesized siRNA molecule, wherein the strand is 26 bp in length and a 742 nt long ds RNA with complete modification with 2'-fluorouracil modifications that resulted in interference. Applicants note that although Parrish taught a 26 bp siRNA molecule, Parrish did not teach *modified* short interfering RNA molecules. Additionally, Applicants respectfully submit that Parrish described 2'-deoxy-2'-fluoro uridine modifications, but not 2'-deoxy-2'-cytidine modifications and further taught that 2'-deoxy modification of cytidine was detrimental to RNAi activity. *See* Parrish, at page 1081, right column ("Modification of cytidine to deoxycytidine … on either the sense or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity."). Furthermore, while Parrish described 2'-deoxy-2'-fluoro modification of uridine in either the sense strand or the antisense strand, there is no description, contrary to the Office's assertion, of this modification simultaneously in both strands, as was first taught by Applicants. *See, e.g.,* Parrish, at page 1081, left column, Figure 5B (describing that interference activities of unc-22 were retained with a 2'-uracil → 2'-fluorouracil in the sense strand and unmodified RNA antisense strand; or with an unmodified RNA sense strand and a modified uracil → 2'-fluoro uracil antisense strand). Parrish does not teach 2'-fluoro modification of cytidines at all. Parrish does not teach 2'-O-methyl modifications. Also, Parrish does not teach double stranded nucleic acids with one or more pyrimidines differentially modified from one or more purines, one of the claim limitations of the instant invention and first taught by Applicants. Finally, Parrish repeatedly noted that activity was more sensitive to modification of the antisense strand than of the sense strand and that depending on the type of modification and location, inactivity could result (*see e.g., id.* at pages 1081, 1082 and 1084), thus confirming that use of "known modifications" from the antisense and ribozyme art had unpredictable results with respect to RNAi activity prior to the teachings of the instant application.

It is further submitted that the Office's summary of Bertrand *et al.* is misleading because the Office failed to mention that Bertrand *et al.* did not achieve comparable results when comparing antisense oligos with siRNAs. For example, Bertrand *et al.* taught that antisense molecules vectorized by dendrimers inhibited the synthesis of stable GFP (Bertrand *et al.*, pg 1002, col. 1); yet no effect on GFP was observed when using siRNAs. (*Id.* at 1003, col. 1). Thus, Bertrand *et al.* showed that one could not use the same practices as applied to antisense oligonucleotides and achieve predictable results with siRNAs.

Likewise, the Office's characterization of Olie *et al.* is misleading. Specifically, the Office failed to note that Olie *et al.* teaches the criticality of the mechanism of action on whether a modified compound is active, as opposed to simply looking at whether the modification confers a known physical attribute, e.g., stability. For example, Olie *et al.* teaches that although phosphorothioate modifications have lower binding affinity to the target mRNA, they also support RNAse H activity and are more resistant to chemical degradation, whereas 2'-O-modifications while providing additional nuclease resistance, generally fail to induce RNAse H to cleave the target mRNA due to formation of RNA-RNA like hybrids. (Olie *et al.*, at 101-102). In fact, to overcome this limitation, as to 2'-O-modifications, it was necessary to include a small number of deoxynucleotides to form a gapmer so that the oligonucleotide possessed a central RNAse H compatible deoxynucleotide window. *Id.* at 102. Consequently, Olie teaches that it is the impact of the modification on the mechanism of action that is critical to activity, not its conference of stability to a molecule. *Id.* at 101-102. *See also,* Kurreck *et al.*. at 1911 ("In contradiction of the literature, a stretch of seven or eight DNA monomers in the center of a chimeric DNA/LNA oligonucleotide is necessary for full activation of RNAse H to cleave the target RNA.")

The Office specifically concluded that one would have been motivated to utilize the same modifications and techniques as antisense and ribozymes because "antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application". (*Id.* at 23.) However, contrary to the Office's allegation, the mechanisms of

action for antisense, ribozymes, and gapmers were known at the time to differ from that of RNAi interference. *See, e.g.*, Bertrand *et al.* at 1000. ("although the final result, the degradation of a target messenger RNA, is identical, the [siRNA] action mechanism in mammalian cells is therefore very different from that of ODN [antisense oligodeoxynucleotides]."). Therefore, one could not incorporate a modification that was known to confer stability to a ribozyme or antisense and apply it to an siRNA molecule with a reasonable expectation that one would obtain an active siRNA. This is further supported by Elbashir *et al.* Elbashir *et al.*, as discussed *supra*, taught that chemical modifications such as 2'-O-methyl and 2'-deoxy modifications, which were successfully applied to such other nucleic acid molecules, must be entirely avoided or applied only to the terminal nucleotides of siRNA molecules.

Third, even disregarding these inaccuracies, the cited references, alone or in combination, do not teach or suggest a nucleic acid duplex specific for CHRM3 RNA having separate strands of 18-27 nucleotides with 50 or more of the nucleotide on each strand modified, wherein the nucleotides are modified with two different 2'-sugar modifications and in particular, where purines nucleotides are differentially modified at the 2'-sugar position from pyrimidine nucleotides at the 2'-sugar position.

Matulic-Adamic *et al.* does not contemplate siRNA or RNA interference, and certainly does not contemplate differential modification strategies. Olie *et al.* (which is not prior art), and Kurreck *et al.* (which is not prior art) teach antisense gapmers that are single stranded and require a deoxy segment for activity. Hence none of these references teach separate strands with 50 to 100 percent modifications on each strand and differential modifications.

Likewise, Elbashir *et al.*, Parrish *et al.*, Bertrand *et al.*, and Braasch *et al.* individually or in combination, do not cure these deficiencies. Elbashir *et al.* teaches away from any modification beyond the four 3'- terminal residues on each strand of a 42 nt duplex and does not suggest or differential 2'-sugar modifications in the same molecule. Parrish *et al.* does not teach chemical modification of short nucleic acid duplexes and fails to teach simultaneous modification of both strands of the duplex. Parrish also fails to teach differential 2'-sugar modifications on a single nucleic acid

molecule. Bertrand *et al.* does not teach 50-100% modification in each strand nor does Bertrand *et al.* teach differential 2'-sugar modifications. Braasch *et al.* teaches LNA incorporation in siRNA and that internal substitutions with LNA can inactive the siRNA. Braasch *et al.* does not teach differential 2'-sugar modifications in a single nucleic acid molecule. Moreover, none of the references teach or suggest differential 2'-sugar modifications between purine and pyrimidine nucleotides.

Subsequent to the decision in *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727 (2007), the Board of Patent Appeals and Interferences ("BPAI") has continued to recognize the criticality of a finding of all the limitations in a claim to establish a *prima facie* case of obviousness. According to the BPAI:

> [A]n examiner must make "a searching comparison of the claimed invention – *including all its limitations* - with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

Ex Parte Wada, BPAI, Appeal 2007-377, page 7 (Jan. 15, 2008) (unpublished). *See also, Ex parte* Shepard, BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished) (BPAI reversed the Examiner's rejection of obviousness, because "having failed to demonstrate that the references teach the limitations of claim 11, the Examiner failed to establish a *prima facie* case of obviousness for claims 17 or 18 which depend from claim 11.")

As discussed *supra*, the references cited do not teach or suggest a double stranded nucleic acid with separate strands having 18-27 nucleotides in each strand wherein i) 50 to 100 percent of the nucleotides in each strand are chemically modified, and ii) any of the purine nucleotides are differentially modified at a 2'-sugar position that differs from any of the pyrimidine nucleotides at a 2'-sugar position. Thus, the cited documents, alone or in combination, fail to show or suggest all of the claim limitations. Accordingly, the Office has not put forth a *prima facie* case of obviousness.

Even assuming *arguendo* that there was a finding or suggestion of all the elements in the prior art, which is not the case, more is required to establish a *prima facie* case of unpatentability due to obviousness. Applicants submit that there was no apparent

reason at the time of filing the instant application to combine the known elements in a fashion that would arrive at the instantly claimed invention. The recent holdings in *KSR Int'l Co. v. Teleflex Inc.* support this position. Recognizing that most true inventions are made with known building blocks, the KSR Court instructed that merely identifying elements of an invention in the prior art is insufficient to establish obviousness. *KSR,* 127 S. Ct. at 1741 ("[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.").

Consistent with this general directive, the Court identified three factors that must be taken into consideration when determining obviousness: (1) whether there is an apparent reason to combine the known elements in a fashion claimed by the patent at issue (*id.* at 1740-41); (2) whether there is a finite number of identified, predictable solutions from the perspective of those skilled in the art (*id.* at 1732); and (3) whether there are teachings in the art that would lead those skilled in the art away from the claimed invention and/or indicate to those skilled persons that similar approaches may not always lead to similar results (*id.* at 1740).

As explained below, at the priority date of the instant claims, there was little if any reason for one of ordinary skill in the art to modify short nucleic acid duplexes in the manner presently claimed, and none of the cited references provides such a reason. Furthermore, the art of chemically modifying a short double stranded nucleic acid was believed to be highly unpredictable at that time not only because the pioneering paper in the field, Elbashir et al., The EMBO Journal, Vol. 20, No. 23 (2001) (as well as the Tuschl reference cited herein), expressly taught away from certain of the claimed modifications but also because modifications suitable for other nucleic acid-based inhibitors were reported to be often unsuitable for short interfering nucleic acid duplexes such as those claimed herein.

Applying the post-*KSR* obviousness standard, Applicants submit that none of the references provides the compelling and apparent reason for those skilled in the art to apply the chemical modification(s) used for other nucleic acid molecules to the claimed constructs.

For example, it is respectfully noted that ribozymes are single-stranded nucleic acid molecules that require at least one stem-loop region, as opposed to the instantly claimed double stranded nucleic acid molecules. Thus, Matulic-Adamic did not teach chemically modified short RNA duplexes because it pertained to modification of ribozymes, which were known to be substantially single-stranded and require at least one stem loop structure for activity. As discussed above, unlike the instantly claimed duplexes, the Matulic-Adamic molecule does not comprise a sense strand and an antisense strand as presently claimed. The reason to modify ribozymes, which are largely single stranded and susceptible to degradation, did not apply to a short double stranded nucleic acid construct, which were known to be substantially more stable. Thus, Matulic-Adamic fails to render the instant claims obvious, either alone or in combination with the other cited references.

Furthermore, none of the references has provided the specific bases required for obviousness when the art, sans the teaching by the instant Applicants, was as unpredictable as it was at the priority date of the instant claims.

Evidence of such unpredictability can be found in at least the cited Elbashir reference. Elbashir allegedly teaches that siRNA molecules may contain terminal end modifications, and at least one modified nucleotide analogue at either the 5' or 3' ends of the siRNA molecule. However, Elbashir does not teach the optimum number and placement of 2'-sugar modifications, such as each pyrimidine is 2 '-deoxy-2'-fluoro nucleotides or each purine is 2'-deoxy or 2'-O-methyl nucleotides or specific terminal cap moieties. With regard to Elbashir, Applicants submit that Elabshir tested and reported on only those molecules wherein each strand contains *a single type* of modification. And among those molecules, when that modification is 2'-deoxy beyond the terminal nucleotides, or 2'-O-methyl anywhere, the RNAi activity is not maintained. Elabshir certainly did not teach a nucleic acid molecule in which any of the purine nucleotides are differentially modified at a 2'-sugar position that differs from any of the pyrimidine nucleotides at a 2'-sugar position.

Importantly, Elbashir demonstrates the impropriety of applying the teachings of the antisense and ribozyme art to siRNA, as well as the unpredictability of the art of chemically modifying short double-stranded nucleic acid molecules at the time of the present invention. Chemical modifications that had been successfully applied to stabilize ribozymes and antisense molecules were found by Elbashir to have limited or no applicability to short nucleic acid duplexes. As discussed previously, Elbashir states that 2'-modified siRNAs comprising minimal modifications at the termini retain RNAi activity, but more extensive modifications beyond the terminal residues are not well tolerated. Indeed, Elbashir comes to this very conclusion in the section entitled, "3.4 The siRNA user guide":

> 2'-deoxy substitutions of the 2-nt 3' overhanging nucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications, however, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNAP assembly.

It is respectfully noted that, grammatically, the term "[m]ore extensive" in the second sentence is and *can only be* intended to modify the term "2-deoxy" and not the term "2-O-methyl" because the latter term does not appear earlier in the same paragraph. This reading is also confirmed by the fact that nowhere in Elbashir is there a disclosure of an active modified double-stranded construct comprising 2'-O-methyl modified nucleotides.

The reasonable conclusion of Elbashir was thus that 2'-deoxy and 2'-O-methyl modifications, which had been previously applied to stabilize single-stranded nucleic acid molecules such as ribozymes and/or antisense molecules, could only be applied to a few terminal residues or not at all if an active short duplex was desired. This was clear evidence that the art of chemically modifying short nucleic acid duplexes was unpredictable. It is important to note that despite the fact that references pertaining to chemical modification of ribozymes (such as Matulic-Adamic) and/or other nucleic acid inhibitors were available to Elbashir *et al.,* these authors nonetheless not only failed to arrive at the claimed modified constructs, but expressly concluded that certain commonplace modifications employed in the antisense and ribozyme art were not applicable to siRNA. Thus, to those of ordinary skill in the art, the results achieved in the

antisense and ribozyme arts were not simply or obviously extendable to RNA interference at the time. This is further proof that the claimed invention could not have been obvious in view of the cited references.

In such an unpredictable environment, then, the cited prior art must teach specifically which modification(s) to use on a double stranded nucleic acid construct that is 21 nucleotides long because an exceedingly large number of possible patterns, types, levels of modification might be generated. None of the cited references here provides the ordinary artisan with reasons to employ exactly the types, levels, and patterns of modifications presently recited so that the resulting constructs may maintain RNAi activity. None of the other references teaches which of the modification patterns, levels and types to employ in a 21-nt duplex, as Applicants have done in the instant application. Thus, the instant claims are not *prima facie* obvious over the cited references.

Accordingly, applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejections.

CONCLUSION

In view of the foregoing remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference would expedite prosecution, she is urged to contact the undersigned before taking further action.

Respectfully submitted,
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